GlaxoWellcome

March 29, 1999

Management Dockets
Dockets Management Branch (HFA-305) 8 '99 MAR 31 A9:48
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket Number: 98D-1168

Dear Sirs:

Please find enclosed GlaxoWellcome's comments on the draft Guidance for Industry-ANDAs: Impurities in Drug Products.

Please feel free to call me at (919) 483-6408 if you need additional information or clarification regarding the comments.

Sincerely,

Suva B. Roy.

Suva B. Roy, Ph. D.
Director, Chemistry Pharmacy and Manufacturing
Regulatory Affairs and Quality Division

98D-1168

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Comments from GlaxoWellcome on the Draft Guidance for Industry
ANDAs: Impurities in Drug Products

General Comments

We agree with the premise that ANDA drug products should follow the ICHQ3B recommendations. We also agree with the proposed limits and thresholds for identification, qualification and reporting of impurities and degradation components in the generic drug products. However, the draft guidance is not clear whether the requirements will be applied retrospectively for already approved ANDAs.

We also propose that the ANDA drug products should follow the ICHQ3C guidance on residual solvents.

Specific Comments

225-234 - The proposed two-fold limit of degradation product compared to the reference listed product (RLD) is too high. There is no established (two-times) rule for setting acceptance criteria for impurities and degradation products from the levels tested. The two-fold limit may result in generic drugs having impurities higher than the qualified level in the RLD. We recommend that the allowable limit for a degradation component be set no higher than the RLD when studied under identical accelerated stability study conditions.

236-242 - While the QSAR database program with its modules can be used to identify the potential toxicity of an impurity, the software has not evolved enough to be used as regulatory tool to establish the safety of a compound. The software is a preliminary prediction tool for research, which requires verification with laboratory data. Applying it as a regulatory tool to justify qualifying an impurity is an immense leap of faith and potentially dangerous. We strongly recommend that scientific literature data or laboratory data support the QSAR finding. We also recommend CDER's Pharmacology/Toxicology experts are consulted regarding the suitability of the QSAR evaluation alone as a regulatory tool. Generally, QSAR alone is not recognized as adequate in the CDER's Pharmacology/Toxicology review practices. We made the same comment to the draft guidance ANDAs: Impurity in Drug Substances.

244-249 - In-vitro genotoxicity studies alone are not sufficient to determine the complete safety profile of a degradation product or impurity. For example, absence of in-vitro genotoxicity may not necessarily prove that the compound is not hepatotoxic. In-vitro genotoxicity should not be the test of last resort to assure the safety of a degradation product. Additional safety studies should be conducted for a full measure of the safety of a compound. Attachment C of the draft guidance provides a list of the minimum safety tests that should be conducted.

We recommend that the decision tree, Attachment B, be amended to delete qualification by in-vitro genotoxicity studies.

250-252 – Lines 250-252 cite Section 505(j) of the FFD&C Act in stating in-vivo toxicity studies cannot be used for generic drug products. The Act does not specifically preclude in-vivo safety/toxicity studies for generic drugs. The Act is silent on the topic. This can be interpreted as in-vivo (animal) safety studies may be performed to qualify new impurities when needed and justified.

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